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PII: S0040-4020(17)31022-0

DOI: 10.1016/j.tet.2017.10.007

Reference: TET 29010

To appear in: *Tetrahedron*

Received Date: 8 August 2017

Revised Date: 2 October 2017

Accepted Date: 5 October 2017

Please cite this article as: Belveren S, Ali Dondas H, Ülger M, Poyraz S, García-Mingüens E, Ferrándiz-Saperas M, Sansano JoséM, Synthesis of highly functionalized 2-(pyrrolidin-1-yl)thiazole frameworks with interesting antibacterial and antimycobacterial activity, *Tetrahedron* (2017), doi: 10.1016/j.tet.2017.10.007.

Graphical Abstract

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Synthesis of highly functionalized 2-(pyrrolidin-1-yl)thiazole frameworks with interesting antibacterial and antimycobacterial activity

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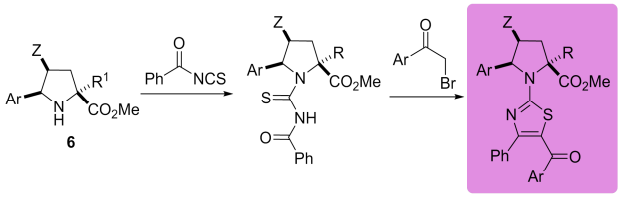

ANTIBACTERIAL AND ANTIMYCOBACTERIAL AGENTS

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Synthesis of highly functionalized 2-(pyrrolidin-1-yl)thiazole frameworks with interesting antibacterial and antimycobacterial activity

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
prolinates
thiazol
antibacterial
antimycobacterial

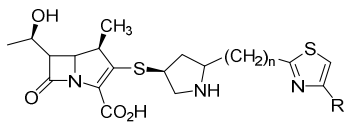
ABSTRACT

A versatile, facile and concise approach to access to highly substituted functionalized 2-(pyrrolidin-1-yl)thiazole ring system is accomplished. The efficient protocol proceeds by the reaction of corresponding racemic or enantiomerically enriched pyrrolidines and readily available benzoylisothiocyanate in acetonitrile followed by sequential reaction of readily available alpha-bromo ketones in acetone. The selectivity and good yield in the desired product is another important advantage of this reaction protocol. In a few cases, the resulting *N*-benzoylthiourea intermediate cyclizes spontaneously before reacting with the benzophenone component. Finally, a wide study of the biological scope of this new bisheterocyclic molecules is reported.

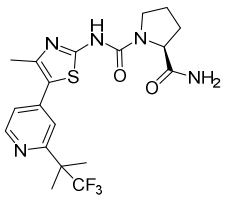
1. Introduction

Pyrrolidine, thiazole and indole ring systems are important structural skeletons found in the structures of various alkaloids, natural compounds, pharmaceuticals, drugs and many other bioactive molecules.[1,2,3,4] The pyrrolidine ring is present in many bioactive compounds and it is useful as building block for the construction of some other biologically important heterocycles.[5,6,7,8] Various chemo-, regio-, and enantioselective reactions, and some versatile tactical combination of the pyrrolidine ring have been reported by us and others.[5,9,10,11,12,13] Hetereocycles bearing thiazole moieties have been extensively studied and reviewed finding a large series of families showing potent bioactivities such as antibiotic, antimycobacterial, anticancer and AchE inhibitory activities.[14,15,16,17,18,19,20] In addition, it is well known that indole skeleton, integrated in natural compound or as part of synthetic molecules, has displayed versatile pharmacological properties such as anticancer,[21] antiviral,[22] anticonvulsant[23] cardiovascular, [24] antidiabetic, antimalarial, antibacterial, anti-inflammatory antifungal activities.[25,26,27]

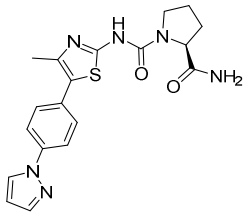
Various compounds containing pyrrolidine and thiazole ring system have been found to be antibacterial agents as structures **1**,[1] and phosphatidylinositol-3-kinase alpha (PI3Ka) inhibitors **2** and **3**. [28,29] Also, general (pyrrolidin-1-yl)thiazole structures **4**, prepared from racemic or D- or L-proline or *trans*-4-hydroxy-L-proline, have been employed for the treatment and/or prevention of KAT (kynurenine aminotransferase) II-associated disorders,[30] as drugs with good antiproliferative activity and epidermal growth factor receptor tyrosine kinase (EGFR-TK) inhibitory activity,[31] and as β_3-adrenergic receptor agonists.[32]



1, n = 0 or 1



2
NVP-BYL 719



3

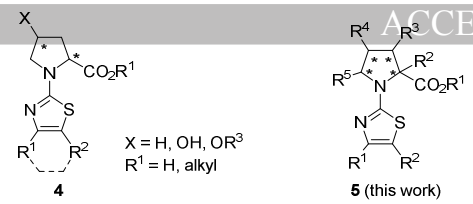
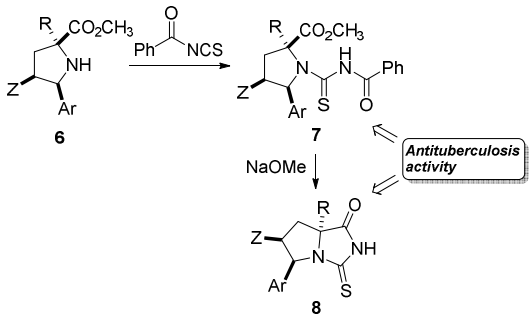


Figure 1. Several biologically important 2-(pyrrolidin-1-yl)thiazole skeletons.

As a continuation of our work regarding the synthesis of aroylaminocarbo-*N*-thioylpyrrolidine **7**, their participation in the formation of several metal complexes,[11,33,34] and the synthesis of thiohydantoin derivatives **8** (Scheme 1),[35] we consider that the combination of both polysubstituted pyrrolidines and thiazole into a new highly functionalized 2-(pyrrolidin-1-yl)thiazole frameworks would be very attractive.

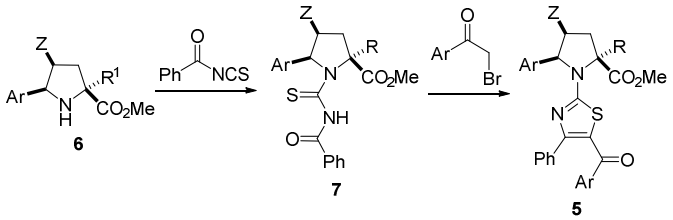


Scheme 1. Synthesis of benzoylaminocarbo-*N*-thioylpyrrolidine and thiohydantoin derivatives from polysusbstituted prolinates **6**.

In this article, we report the synthesis of molecules bearing polysubstituted pyrrolidine-thiazole heterocycles from readily available starting materials. In many cases, the incorporation of another heterocyclic system such as indole resulted to be beneficial since the biological point of view. Their antibacterial activity against a range of Gram-positive and Gram-negative bacteria and their antimycobacterial activity against M. tuberculosis H37Rv strain were also tested.

2. Results and Discussion

For the synthesis of 2-(pyrrolidin-1-yl)thiazoles **5** the polysubstituted pyrrolidines **6** were allowed to react with *N*-benzoyl isothiocyanate affording intermediate benzoylaminocarbo-*N*-thioylpyrrolidines **7**,[35] which was transformed into the corresponding heterocycles **5** with α-bromobenzophenones in refluxing acetone.[36]



Scheme 2. General synthetic design for the preparation of **5**.

Firstly, we employed enantiomerically enriched prolinate derivatives with the aim to obtain reliable biological data for each enantiomer. Thus, prolinates **6a-i** (Figure 2), prepared in in different er (see experimental part), through a catalytic enantioselective 1,3-DC according to the published procedures in very high enantiomeric ratio (see experimental part), were submitted to the addition reaction onto *N*-benzoyl isothiocyanate in dry acetonitrile at room temperature for 24 h affording benzoylaminocarbo-*N*-thioylpyrrolidines **7** in almost quantitative yields. Without any other purification these intermediate products **7** were immediately (in order to prevent spontaneous cyclizations) allowed to react with 2-bromo-4′-methoxyacetophenone in refluxing acetone for 48 h (Scheme 3 and Table 1).

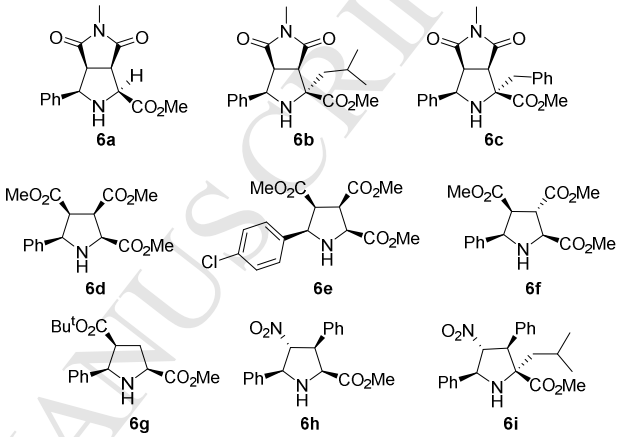
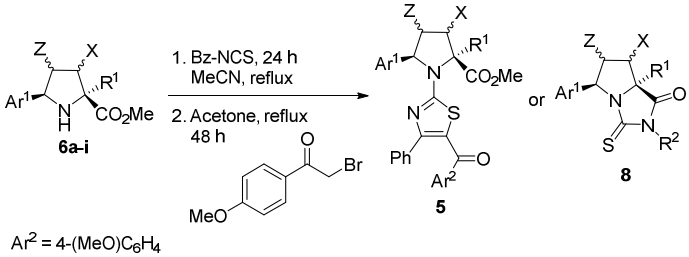


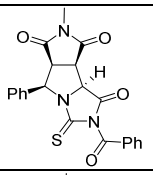
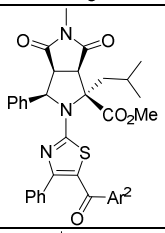
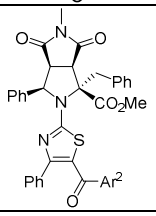
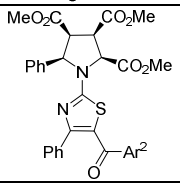
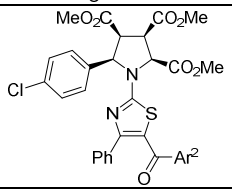
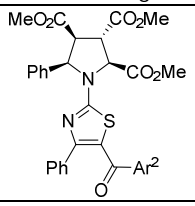
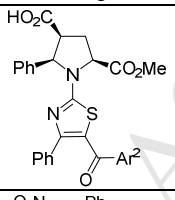
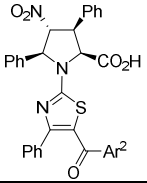
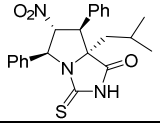
Figure 2. Enantiomerically enriched pyrrolidines **6** employed in the synthesis of 2-(pyrrolidin-1-yl)thiazoles **5**.

The behavior of all starting prolinate derivatives **6** (Figure 2) was not predictable. For example, *N*-Methylmaleimide (NMM) derivatives bearing a substituent in R^1 (different to hydrogen) afforded the desired thiazoles in good overall yields (Table 1, entries 2 and 3). However, in the reaction of **6a** (R^1 = H, Ar^1 = Ph) the cyclization of the intermediate (non-isolated) benzoylaminocarbo-*N*-thioylpyrrolidine **7a** occurred rapidly furnishing *N*-benzoylthiohydantoin *N*-Bz-**8a** in 81% yield (Table 1, entry 1). Enantiomerically enriched prolinates **6d**-**6h** afforded their corresponding products **5** or **5'** in moderate to good yields (Table 1, entries 4-8). In a couple of examples we detected the unexpected hydrolysis of the *tert*-butyl ester (compound **5g'**) and the methyl ester (compound **5h'**) under this reflux of wet acetone obtaining in these two examples the lowest yields of this series. Another example of fast cyclization occurred during the reaction of the highly substituted nitroprolinate **6i** which afforded the *N*-debenzoylated thiohydantoin **8i** in excellent 95% yield (Table 1, entry 9). In all these examples the absolute configuration was retained.



Scheme 3. Two-step process to access enantiomerically enriched heterocycles **5**.

Table 1. Synthesis of enantiomerically enriched 2-(pyrrolidin-1-yl)thiazoles **5**

Entry	**6**	Product	No.	Yield (%)[a]
1	**6a**		*N*-Bz-**8a**	81
2	**6b**		**5b**	60
3	**6c**		**5c**	62
4	**6d**		**5d**	68
5	**6e**		**5e**	82
6	**6f**		**5f**	64
7	**6g**		**5g'**	43
8	**6h**		**5h'**	34
9	**6i**		**8i**	95

[a] Isolated combined yield from cycloadducts **6** after flash chromatography.

This series of 2-(pyrrolidin-1-yl)thiazoles **5** resulted to be time- and temperature sensitive and after two days storage at 25 ºC large decompositions were detected. According to previous results and tests, the combination of a suitable dipolarophile together with the introduction of a (3-indolyl)methyl, phenyl or benzyl substituent as R^1 in molecules **6** (Scheme 3) would ensure a high stability of the resulting both benzoylaminocarbo-*N*-thioylpyrrolidines **7** and thiazoles **5**. It is known, for example, that it was not an easy task to cyclize the corresponding indolyl derivatives to thiohydantoins **8**,[34] but when we tried to synthesize the optically pure compound **6j**[37] the corresponding enantiomeric ratio was very poor.

Next, the preparation of several selected racemic cycloadducts (which could not be obtained as enantiomerically pure form) **6j-6o** depicted in Figure 3 was carried out via thermal or metal-catalyzed 1,3-DC (see experimental part) and, immediately, they were submitted to the reaction with benzoylisothiocyanate affording benzoylaminocarbo-*N*-thioylpyrrolidines **7**. These compounds **7**, obtained in very good yields (80-92%, Table 2, entries 1-6) were stable and could be purified by flash chromatography detecting the appearance of rotamers in several samples. Analogously, the stability of the racemic thiazole derivatives was also appropriate to study their biological properties. Upon reaction of **7** with 2-bromo-4′-methoxyacetophenone for 24-48 h in refluxing acetone, 2-(pyrrolidin-1-yl)thiazoles **5j-o** were generated in 65-83 yields (Table 2, entries 1-6).

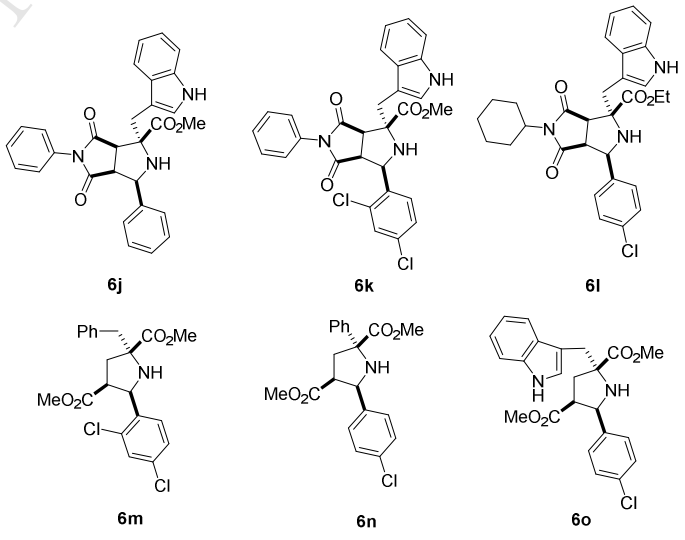
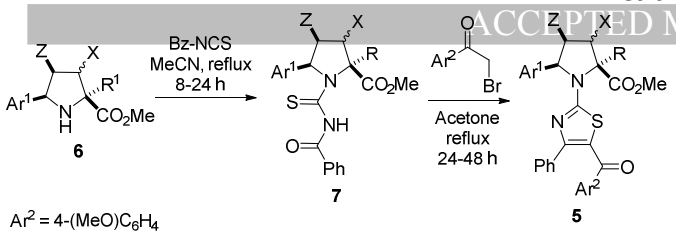
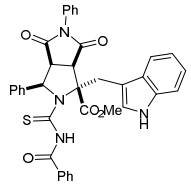
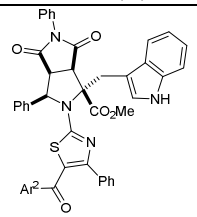
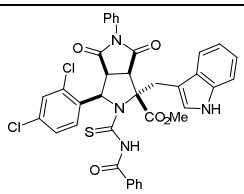
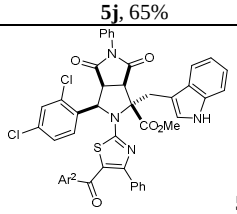
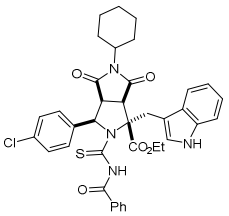
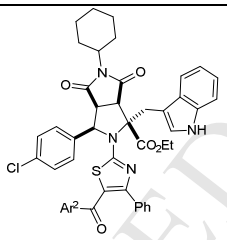
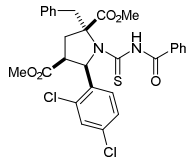
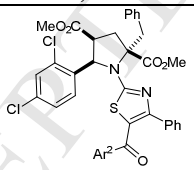
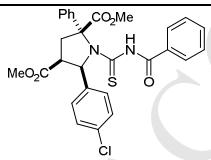
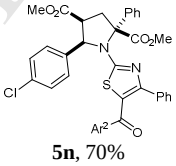
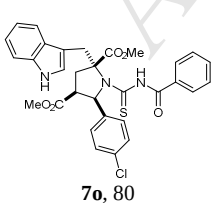
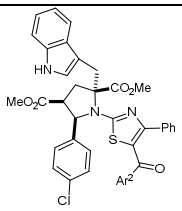


Figure 3. Racemic *endo*-pyrrolidines **6** employed in the synthesis of 2-(pyrrolidin-1-yl)thiazoles **5**.



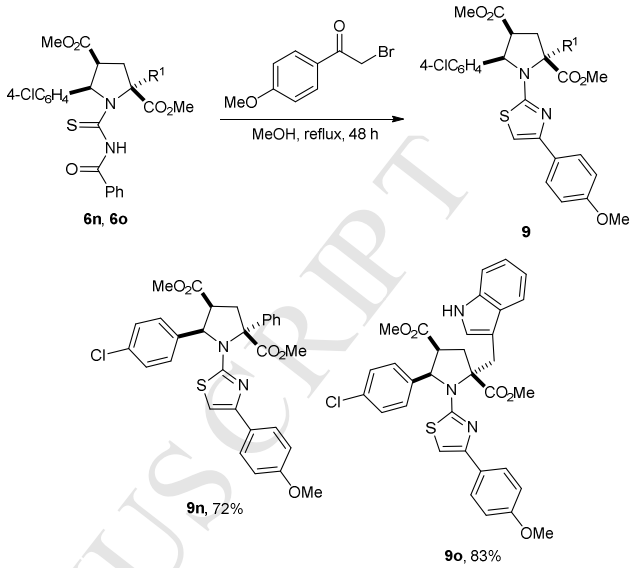
Scheme 3. Synthesis of racemic benzoylaminocarbo-*N*-thioylpyrrolidines **7** and thiazoles **5**.

Table 2. Synthesis of enantiomerically enriched 2-(pyrrolidin-1-yl)thiazoles **5**

Ent.	**6**	Product **7**, Yield (%)[a]	Product **5**, Yield (%)[a]
1	**6j**	 **7j**, 86%	 **5j**, 65%
2	**6k**	 **7k**, 85	 **5k**, 82%
3	**6l**	 **7l**, 80	 **5l**, 76%
4	**6m**	 **7m**, 89	 **5m**, 83%
5	**6n**	 **7n**, 92%	 **5n**, 70%
6	**6o**	 **7o**, 80	 **5o**, 75%

[a] Isolated combined yield from after flash chromatography. Ar^2 = 4-(MeO)C_6H_4.

The thiazole synthesis was very sensitive to the protic character of the solvent employed. Thus, when anhydrous methanol was used instead of acetone 2,3-disubstituted thiazoles **9n** and **9o** were generated in 72 and 83 % yield, respectively, as consequence of a previous debenzoylation of the starting compound **6n** or **6o** and subsequent nucleophilic attack of the sulfur atom followed by cyclization (Scheme 4).



Scheme 4. Synthesis of racemic thiazoles **9n** and **9o**.

Anti-tuberculosis (TB) activity: Anti-TB activity of the tested compounds was performed according to literature method utilizing Microplate Alamar Blue assay.[38] The compounds **6m**,**j**,**l**, **7l**,**m**,**n**, **5m**,**k**,**l** and **9o** were screened against *M. tuberculosis* H37Rv strain and measured by means of MIC values (µg/cm^3). Ethambutol (EMB) (Sigma E4630) and isoniazid (INH) (Sigma I3377) were used as standard reference drugs. The activity of the tested compounds (Table 3), showed moderate to good activity, in the range of 3.90-62.5 µg/ml^3 when compared to isoniazid and ethambutol as known active reference drugs. In some cases better activity than known reference ethambutol. The compounds **7k**,**l**,**m** revealed the highest activities with the MIC values 3,90-7.81 µg/ml whereas the compound **6j** showed a moderate activity value of 20 µg/mL and **6f** and **7n** showed a moderate activity values 31.25 µg/ml and the others compounds showed the lowest activities with the MIC values 62.5 µg/ml. Chiral compounds **5b-h'** were not tested due to their instability. Although the mode of action or biological target of these molecules is unknown at the moment.

The indicated target compounds in the Table 3 inhibited the growth of bacteria at minimum inhibitory concentrations (MIC) values in the range of 62.5 -500 μg/ml. The control, ampicillin, showed activity against the tested *bacteria* with a range of 125-0.9 μg/mL.of MIC values.

Antibacterial Activity: Stock solutions were prepared by dissolving the tested compounds in DMSO and then diluting in Mueller-Hinton broth and Triptic soy broth and the test medium were prepared at concentrations of 500, 250, 125, 62.5, 31.25, 15.62, 7.8, 3.9 and 1.9 µg mL-1. The minimum inhibitory concentrations (MIC) values was determined by agar dilution in duplicate as recommended by the Clinical Laboratory Standards Institute39 To ensure that the solvents had no effect on microbial growth, a control test was performed containing inoculated broth

supplemented with DMSO at the same dilutions used for the test compounds and was determined to be inactive. The minimum inhibitory concentrations (MIC) for each compound were investigated against standard bacterial strains: Staphylococcus aureus (ATCC 25925), Escherichia coli (ATCC 25923), Acinetobacter baumanii (ATCC 02026), Bacillus subtilis (ATCC 6633) and Aeromonashydrophila (ATCC 95080) obtained from the Refik Saydam Hıfzısıhha Institute, Ankara, Turkey. Ampicillin was used as control drug. The observed data on the antibacterial activity of the compounds and the control drug are given in Table 3.

3. Conclusions

Two different types of thiazole derivatives can be obtained depending on the solvent employed. It was not predictable the behavior of benzoylaminocarbo-*N*-thioylpyrrolidines because the spontaneous cyclization cannot be controlled at all. The nature of this process is strongly dependent of the substituents at 2, 3 and 4-positions of the prolinate. The screened compounds showed moderate antibacterial activity against various bacteria strains, in addition showed good anti-TB activity against *M. tuberculosis* H37Rv strain, the target compounds showed better activity than the antibacterial results but moderate activity when compared to isoniazid and ethambutol as known reference drugs (Table 1). It is remarkable that the highst activity corresonded to **6o**, **7o** and **9o**, which posses *p*-chlorophenyl-methoxycarbonyl-[3-indolylmehyl] common substituents around pyrrolidine nucleus. Further research regarding the incorporation of these type compounds to another scaffolds ıs under investigation and their biological activity will be reported in due course.

4. Experimental Section

4.1. General information

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Mass spectra were recorded at 70 eV on a VG Autospec mass spectrometer. Nuclear magnetic resonance spectra and decoupling experiments were determined at 250 MHz on a Q.E 300 instrument, at 300 MHz on a Bruker Avance AC-300 and at 500 MHz on a Bruker AM500 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in $CDCl_3$ except where otherwise stated. The structurally most important peaks of the IR spectra (recorded using a Nicolet 510 P-FT-ATR) are listed and wavenumbers are given in cm^{-1}. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF254 (Merck 7730). Petroleum ether refers the fraction with bp 40-60 ºC unless otherwise specified. Specific optical rotations were measured in a JASCO polarimeter 2000-series. HPLC analysis was performed employing chiral stationary phase columns in a JASCO 2000 series. Microanalyses were obtained using a Carlo-Erba Model 1106 instrument. Chiral compounds **6a** (99:1 er),[39] **6b** (96:4 er),[39] **6c** (99:1 ee),[39] **6d** (85:15 er),[40] **6e** (85:15 er),[40] **6f** (91:9 er), **6g** (75:25 er),[40] **6h** (99%, ee),[41] **6i** (99% ee),[41] were prepared according to published procedures. The known racemic pyrrolidines and *N*-aminocarbothiolpyrrolidines **6j**,[42,43] **6m**,[35] **6n**,[34] **7m**[35] were prepared according to published procedures. Novel compounds were prepared by following the general procedures given below.

4.2. Synthetic procedures and characterization data

*4.2.1. General procedure for the synthesis of enantiomerically enriched compounds **5b-f**, **5g'**, **5h'**, N-Bz-**8a** and **8i**.*

In a flask containing the corresponding prolinate **6a-i** (0.5 mmol) in dry acetonitrile (10 mL) *N*-benzoylisothiocyanate (64 μL, 0.5 mmol) was added and the resulting solution was stirred under reflux for 24 h. The solvent was evaporated and the crude mixture was analysed by ^{1}H NMR. At this point the presence of compounds *N*-Bz-**8a** and **8i** was observed. For the other examples, the crude compound was immediately dissolved in dry acetone (10 mL) containing 2-bromo-4′-methoxyacetophenone (115 mg, 0.5 mmol) and the mixture refluxed for 48 h. The solvent was evaporated under reduced pressure to give a sticky oil which was purified by column chromatography (flash silica) obtaining compounds **5** or **5'**.

*4.2.1.1. (5R,5aS,8aR,8bS)-2-benzoyl-7-methyl-5-phenyl-3-thioxohexa-hydropyrrolo[3',4':3,4]pyrrolo[1,2-c]imidazole-1,6,8(7H)-trione: (N-Bz-**8a**).* White solid (169.9 mg, 81 % yield); mp 205-209 ºC; $[\alpha]_D^{30}$ = -3.3 (*c* 1, DMSO, 99:1 er); IR υ_{max}: 3343, 1745, 1702, 1530 cm^{-1}; ^{1}H NMR (300 MHz, DMSO) δ: 7.15-7.65 (m, 10H, Ar*H*), 5.81 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 10.1 Hz, 1H), 4.08-4.33 (m, 2H), 3.72 (s, 3H, NCH_3); ^{13}C NMR (DMSO) δ: 181.4, 174.5, 173.0, 168.3, 164.7, 136.8 (Ar*C*), 132.7, 132.3, 128.2, 128.1, 127.9, 127.8, 127.3, 99.5, 52.2 (CH), 49.9 (CH), 46.2 (CH), 40.7 (CH), 24.1 (CH_3); MS (EI): *m/z* 288 (M^+-$C_8H_3O_2$, 12%), 230 (15), 229 (96), 178 (11), 177 (96), 167 (16), 149 (45), 146 (19), 145 (22), 144 (65), 143 (17), 142 (10), 118 (15), 117 (100), 116 (12), 115 (25), 112 (11), 105 (43), 91 (13), 90 (13), 84 (53), 83 (11), 77 (26), 71 (16), 70 (14), 66 (58), 57 (25), 55 (15), 51 (11), 44 (34), 43 (43), 41 (12); HRMS (DIP): *m/z* calculated for $C_{22}H_{17}N_3O_4S$: 419.0940, found: 419.0961.

*4.2.1.2. Methyl (1S,3R,3aS,6aR)-1-isobutyl-2-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5b**):* Yellow oil (191.2 mg, 60 % yield); $[\alpha]_D^{29}$ = 26.3 (*c* 0.8, $CDCl_3$, 96:4 er); IR υ_{max}: 2954, 1741, 1708, 1596, 1508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.68 (m, 6H), 7.25-7.3 (m, 3H), 6.99-7.16 (m, 3H), 6.55 (d, *J* = 8.9 Hz, 2H), 5.27 (d, *J* = 10.8 Hz, 1H), 4.10 (dd, *J* = 10.8, 9.1 Hz, 1H), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.58 (d, *J* = 9.1 Hz, 1H), 3.07 (dd, *J* = 15.1, 7.4 Hz, 1H), 2.69 (s, 3H, NCH_3), 2.22 (dd, *J* = 15.1, 3.5 Hz, 1H), 1.64 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H, CH_3), 0.77 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 187.7, 174.5, 173.1, 171.1, 164.9 (ArC), 162.7, 155.6, 135.2, 134.7, 131.9, 130.0, 129.0, 128.5, 127.7, 124.6, 113.1, 75, 68.9 (CH), 55.4 (CH_3), 54.4 (CH_3), 53.0 (CH), 50.9 (CH), 42.7 (CH_2), 25.9 (CH_3), 24.9 (CH_3), 24.1 (CH_3), 23.7 CH); MS (EI): *m/z* 637 (M+, <2%), 582 (26), 581 (69), 578 (14), 549 (15), 522 (27), 399 (15), 385 (11), 135 (100), 133 (11), 77 (12); HRMS (DIP): *m/z* calculated for $C_{36}H_{35}N_3O_6S$: 637.2242, found: 637.2239.

*4.2.1.3. Methyl (1S,3R,3aS,6aR)-1-benzyl-2-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3-phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5c**):* Yellow oil (208.2 mg, 62 % yield); $[\alpha]_D^{30}$ = 66.0 (*c* 0.6, $CDCl_3$, 99:1 er); IR υ_{max}: 2951, 1744, 1703, 1597 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ mixed rotamers: 7.48 (d, *J* = 6.0 Hz, 4H, Ar*H*), 7.33 (m, 10H, Ar*H*), 7.10 (m, 18H, Ar*H*), 6.57 (d, *J* = 6.0 Hz, 4H, Ar*H*), 4.86 (d, *J* = 6.0 Hz, 1H, major rotamer), 4.59 (d, *J* = 12 Hz, minor rotamer), 4.54 (d, *J* = 9.0 Hz, 1H, major rotamer), 4.00 (s, 6H, both rotamers), 3.89 (s, 3H, minor rotamer), 3.72 (s, 3H, major rotamer), 3.66 (d, *J* = 6.0 Hz, 1H minor rotamer), 3.52 (dd, *J* = 6.0, 6.0 Hz, minor rotamer), 3.49 (d, *J* = 12.0 Hz, minor rotamer), 3.44 (d, *J* = 6.0 Hz, 1H, major rotamer), 3.37 (d, *J* = 9.0

Hz, 1H, major rotamer), 3.10 (d, *J* = 12.0 Hz, 1H, minor rotamer), 2.79 (s, 3H, major rotamer), 2.66 (dd, *J* = 9.0, 6.0 Hz, 1H, mayor rotamer), 2.60 (s, 3H, minor rotamer); ^{13}C NMR ($CDCl_3$): δ mixed rotamers: 187.8 (CO), 175.6 (Ar*C* and CO), 174.6, 174.3, 173.2, 171.3, 170.2, 165.1, 162.8, 155.9, 135.8, 135.0, 134.6, 132.0, 130.4, 130.3, 130.1, 129.7, 129.4, 129.3, 129.1, 128.7, 128.6, 128.1, 127.7, 127,3, 125.6, 124.9, 113.2, 75.4 (C), 71.3, 69.1 (CH), 61.4, 55.5 (ArO*Me*), 55.3, 54.2 (CO_2*Me*), 53.8, 53.1 (CH), 52.5, 49.9 (CH), 49.5, 40.4 (CH_2), 39.2, 24.9 (CH_3), 24.6; MS (EI): *m/z* 671 (M^+, 16%), 582 (12), 581 (36), 580 (100), 464 (10), 463 (32), 437 (10), 399 (21), 135 (95), 115 (13), 91 (20), 77 (13); HRMS (DIP): *m/z* calculated for $C_{39}H_{33}N_3O_6S$: 671.2090, found: 671.2086.

*4.2.1.4. Trimethyl (2S,3R,4S,5R)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-5-phenylpyrrolidine-2,3,4-tricarboxylate (**5d**):* Yellow oil (209.0 mg, 68 % yield); $[\alpha]_D^{31}$ = 12.4 (*c* 1, $CDCl_3$, 85:15 er); IR υ_{max}: 2952, 1737, 1596, 1509, 1473 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.54 (m, 4H, Ar*H*), 7.22-7.37 (m, 5H, Ar*H*), 6.99-7.14 (m, 3H, Ar*H*), 6.54 (d, *J* = 9.0 Hz, 2H, Ar*H*), 5.63 (d, *J* = 8.3 Hz, 1H), 5.05 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.64-3.77 (m, 2H), 3.18 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 187.7 (C), 169.9 (C), 169.4 (C), 168.4 (C), 162.6 (Ar*C*), 156.0, 134.6, 134.0, 131.8, 131.6, 130.2, 130.0, 129.3, 128.7, 128.6, 127.8, 127.7, 127.5, 124.8, 113.0, 68.46 (CH), 63.6 (CH), 55.4 (CH_3), 52.7 (CH_3), 52.4 (CH_3), 51.6 (CH_3), 51.2 (CH), 47.7 (CH); MS (EI): *m/z* 615 (M^++ H^+, 16%), 614 (42), 556 (16), 555 (44), 463 (15), 412 (14), 411 (52), 393 (18), 135 (100), 133 (12), 121 (11), 115 (11), 77 (16); HRMS (DIP): *m/z* calculated for $C_{33}H_{30}N_2O_8S$: 614.1723, found: 614.1719.

*4.2.1.5. Trimethyl (2S,3R,4S,5R)-5-(4-chlorophenyl)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)pyrrolidine-2,3,4-tricarboxylate (**5e**):* Yellow oil (266.2mg, 82 % yield); $[\alpha]_D^{30}$ = -2.3 (*c* 1, $CDCl_3$, 85:15 er); IR υ_{max}: 2951, 1741, 1596, 1508 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42-7.50 (m, 3H, Ar*H*), 7.32-7.38 (m, 2H, Ar*H*), 7.22-7.30 (m, 3H, Ar*H*), 7.02-7.17 (m, 3H, Ar*H*), 6.56 (d, *J* = 8.8 Hz, 2H, Ar*H*), 5.60 (d, *J* = 7.9 Hz, 1H), 5.08 (d, *J* = 6.6 Hz, 1H), 3.89 (s, 3H, OCH_3), 3.7 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.65-3.76 (m, 2H), 3.26 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 187.5 (C), 169.8 (C), 169.2 (C), 168.3 (C), 168.1 (Ar*C*), 162.8, 134.6, 134.0, 132.8, 131.9, 130.1, 130.0, 129.4, 128.9, 128.8, 127.8, 124.8, 113.1, 67.8 (CH), 64.0 (CH), 55.4 (CH_3), 52.9 (CH_3), 52.5 (CH_3), 51.8 (CH_3), 51.0 (CH), 47.9 (CH); MS (EI): *m/z* 650 (M^++ H^+, 12%), 649 (11), 648 (27), 591 (11), 589 (26), 447 (16), 446 (12), 445 (41), 393 (18), 135 (100), 77 (11); HRMS (DIP): *m/z* calculated for $C_{33}H_{29}ClN_2O_8S$: 648.1333, found: 648.1348.

*4.2.1.6. (2S,3S,4R,5S)-1-(5-(4-Methoxybenzoyl)-4-phenylthiazol-2-yl)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (**5f**):* Yellow oil (196.7 mg, 64% yield); $[\alpha]_D^{28}$ = 47.5 (*c* 0.7, $CDCl_3$, 91:9 er); IR υ_{max}: 2929, 2852, 1740, 1597, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04-7.64 (m, 12 H, Ar*H*), 6.54 (d, *J* = 8.9 Hz, 2H, Ar*H*), 5.18 (d, *J* = 7.3 Hz, 1H), 5.01 (d, *J* = 8.1 Hz, 1H), 4.02-4.05 (m, 2H), 3.94 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 187.6 (C), 170.9 (C), 170.5 (C), 168.8 (C), 166.6 (Ar*C*), 162.8, 135.2, 134.0, 131.9, 130.2, 129.2, 129.0, 128.8, 128.3, 128.1, 127.8, 124.7, 113.2, 100.13, 67.8 (CH), 65.3 (CH), 55.5 (CH_3), 53.2 (CH_3), 53.1 (CH_3), 52.4 (CH_3), 52.2 (CH), 48.0 (CH); MS (EI): *m/z* 615 (M^+ + H^+, 15%), 614 (43), 555 (23), 495 (28), 464 (12), 463 (37), 411 (34), 393 (28), 135 (100), 133 (13), 77 (15); HRMS (DIP): calculated for ($C_{33}H_{30}N_2O_8S$): 614.1723, found, 614.1729.

*4.2.1.7. (2R,3S,5S)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-5-(methoxycarbonyl)-2-phenylpyrrolidine-3-carboxylic acid (**5g'**):* Yellow oil (116.7 mg, 43% yield); $[\alpha]_D^{29}$ = -37.5 (*c* 0.6, $CDCl_3$, 75:25 er); IR υ_{max}: 2948, 1743, 1597, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.81-7.87 (m, 12H, Ar*H*), 6.54 (d, *J* = 9 Hz, 2H, Ar*H*), 5.12 (d, *J* = 8.9 Hz, 1H), 4.78 (dd, *J* = 10.2, 6.7 Hz, 1H), 3.89 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.62-3.77 (m, 1H), 2.75 (m, 1H), 2.55 (dt, *J* = 13.1, 6.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 187.7 (C), 172.54 (C), 171.8 (C), 167.0 (Ar*C*), 162.8, 155.3, 135.4, 133.8, 132.5, 131.9, 130.2, 130.1, 129.0, 128.9, 128.8, 128.2, 127.8, 127.5, 124.1, 113.2, 68.3 (CH), 62.8 (CH), 55.5 (CH_3), 52.9 (CH_3), 49.5 (CH), 30.6 (CH_2); MS (EI): *m/z* 543 (M^++ H^+, 19%), 542 (56), 484 (15), 483 (46), 411 (31), 337 (11), 336 (12), 335 (11), 334 (14), 333 (12), 135 (100), 133 (13), 129 (11), 107 (11), 89 (10), 77 (19); HRMS (DIP): *m/z* calculated for $C_{30}H_{26}N_2O_6S$: 542.1512, found: 542.1520.

*4.2.1.8. (2S,3S,4R,5S)-1-(5-(4-Methoxybenzoyl)-4-phenylthiazol-2-yl)-4-nitro-3,5-diphenylpyrrolidine-2-carboxylic acid (**5h'**):* Yellow oil (102.9 mg, 34% yield); $[\alpha]_D^{31}$ = -24.1 (*c* 0.5, $CDCl_3$, 99:1 er); IR υ_{max}: 2959, 2945, 2926, 2852, 1740, 1598, 1557, 1509 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.09-7.72 (m, 17H, Ar*H*), 6.55 (d, *J* = 8.9Hz, 2H, Ar*H*), 5.90 (dd, *J* = 11.9, 8.6 Hz, 1H), 5.72 (d, *J* = 9.3 Hz, 1H), 5.31 (d, *J* = 8.6 Hz, 1H), 4.63 (dd, *J* = 11.9, 9.3 Hz, 1H), 3.72 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$) δ: 192.5 (C), 166.5 (C), 132.0 (Ar*C*), 130.2, 129.9, 129.4, 129.3, 129.2, 128.4, 128.1, 128.0, 127.8, 114.4, 113.9, 113.6, 113.3, 113.2, 93.0 (CH), 66.8 (CH), 55.5 (CH_3), 50.8 (CH), 29.9 (CH); MS (EI): *m/z* 514 (M^+ – $CHNO_4$, 11%), 513 (30), 512 (30), 235 (37), 193 (25), 191 (14), 135 (100), 115 (22), 107 (11), 92 (12), 90 (12), 77 (28); HRMS (DIP): calculated for $C_{33}H_{26}N_2O_2S$ [M^+ – $CHNO_4$], 514.1715 found, 514.1732.

*4.2.1.9. (5S,6R,7S)-5,7-difenil-6-nitro-3-tioxohexahidro-1H-pirrolo[1,2-c]imidazol-1-one (**8i**):* Yellow foam (194.5 mg, 95%); $[\alpha]_D^{26}$ = -42.7 (*c* 1, $CHCl_3$, 99:1 er); IR υ_{max}: 2954, 2925, 1723, 1697, 1557, 1505 cm^{-1}; ^{1}H RMN (300 MHz, $CDCl_3$) δ_H: 7.05-7.44 (m, 10H, Ar*H*), 5.86 (t, *J* = 10.7 Hz, 1H), 5.70 (d, *J* = 9.5 Hz, 1H), 4.52 (d, *J* = 12.1 Hz, 1H), 3.17 (dd, *J* = 15.6, 4.1 Hz, 1H), 2.19 (m, 1H), 2.19 (dd, *J* = 15.4, 4.6 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H, CH_3), 1.06 (d, *J* = 6.7 Hz, 3H, CH_3); ^{13}C RMN ($CDCl_3$) δ: 178.3 (C), 162.6 (C), 135.8 (Ar*C*), 133.2, 132.5, 130.6, 129.6, 129.5, 129.3, 129.1, 128.8, 127.7, 92.4 (CH), 79.2 (C), 72.7 (CH), 53.9 (CH), 52.5 (CH), 36.0 (CH_2), 25.9 (CH_3),; MS (EI): *m/z* 409 (M+-46, <2%), 366 (21), 276 (24), 194 (16), 193 (100), 115 (32), 105 (63), 77 (26); HRMS (DIP): calculated for $C_{19}H_{16}NOS$ [M^+ –$C_3H_7NO_2$], 367.1561, found, 367.1576.

*4.2.2. General procedure for the synthesis of pyrrolidines (**6k**,**l**,**o**)*.

Method A: The solution of the corresponding dipolarophile (1 mmol) in dry toluene (15 mL) was added to a stirred solution of the imine (1 mmol) in dry toluene (15 mL). The resulting mixture was stirred at reflux temperature for 32-48 h and purified by crystallization or column chromatography.

Method B: To a stirred solution of imine (1 mmol) in dry toluene (15 ml) was added Et_3N (0.23 mL, 1.7 mmol) and Ag_2O (0.058 mg 0.25 mmol). The reaction mixture was stirred for 10 minutes and the corresponding dipolarophile (1 mmol) in dry toluene (15 mL) was added. The resulting mixture was stirred at room temperature for 26 h and quenched with saturated aqueous NaCl and NH_4Cl, extracted with DCM, dried over $MgSO_4$, and purified by column chromatography.

4.2.2.1. Methyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-3-(2,4-dichlorophenyl)-4,6-dioxo-5-*

phenyloctahydropyrrolo[3,4-c]pyrrole-1-carboxylate ***(6k)***: White solid (400 mg, 73 % yield); mp 311-313 ºC (from EtOAc:hexane, decomp.); IR ν_{max}: 3379, 2952, 1777, 1739, 1713,1586 cm^{-1}. ^1H NMR (400 MHz, DMSO) δ_H: 10.25 (br.s, 1H, NH), 7.80-7.02 (m, 13H, Ar*H*), 5.42 (dd, *J* = 9.3 Hz, 4.60 Hz, 1H), 4.19 (dd, *J* = 9.3 Hz, 7.73 Hz, 1H), 3.93 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H), 3.78 (s, 3H, OCH_3), 3.73 (d, *J* = 14.4 Hz, 1H), 3.60 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ_C: 174.9, 173.5, 171.6 (CO), 136.3, 136.0, 134.1, 132.5, 132.0, 129.3, 128.8, 128.2, 127.5, 126.9, 126.6, 124.4, 121.0, 118.5, 118.6, 117.9, 111.5, 107.6, 70.3, 56.4, 53.2, 51.6, 46.7, 30.6. MS (EI): *m/z* (ESI): 548.1 ($M+H^+$, 100), 549 ($M+H^+$, 33). HRMS (DIP): calculated for ($C_{29}H_{23}Cl_2N_3O_4$): 547.1076, found, 547.1070.

4.2.2.2. Ethyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-3-(4-chlorophenyl)-5-cyclohexyl-4,6-dioxo-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate* ***(6l)****:* White solid (422 mg, 79 %); mp 245-247 ºC (from EtOAc:hexane); IR ν_{max}: 3353, 3058, 2932, 1761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.25 (br. s, 1H, NH), 7.56 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.31-6.99 (m, 8H, Ar*H*), 4.84 (dd, *J* = 8.7 Hz, 2.2 Hz, 1H), 4.31-4.19 (m, 2H), 3.81-3.72 (m, 1H), 3.61 (d, *J* = 14.6 Hz, 1H), 3.38 (d, *J* = 7.6 Hz, 1H), 3.23 (d, *J* = 14.5 Hz, 1H), 2.46 (s, 1H, NH), 2.02-0.83 (m, 11H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 175.6, 174.6, 171.6 (CO), 136.3, 135.9, 133.8, 128.8, 128.4, 127.8, 123.1, 122.3, 119.8, 118.2 111.4, 109.3, 71.1, 61.6, 60.6, 53.7, 52.0, 48.8, 30.7, 28.9, 28.3, 25.7, 24.8, 14.1; MS (EI): *m/z* 534 ($M+H^+$, 100), 536 ($M+H^+$, 35); HRMS (ESI): calculated for $C_{30}H_{33}ClN_3O_4$: $[MH]^+$ 534.2160, found 536.2153.

4.2.2.3. Dimethyl (2R,4S*,5R*)-2-[(1H-indol-3-yl)methyl]-5-(4-chlorophenyl)pyrrolidine-2,4-dicarboxylate* ***(6o)***: White solid (363 mg, 85%); mp 169-171 ºC (from EtOAc:hexane); IR ν_{max}: 3398, 3304, 2955, 2924, 1727, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H : 10.90 (s, 1H, NH), 7.52 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.34-6.94 (m, 8H, Ar*H*), 4.73 (t, *J* = 7.9 Hz, 1H), 3.59 (s, 3H, OCH_3), 3.43 (dd, *J* = 15.6 Hz, 7.5 Hz, 1H), 3.20-3.08 (m, 6H), 2.15 (dd, *J* = 13.3, 7.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ_C: 175.1, 172.1 (CO), 140.3, 135.8, 131.4, 128.7, 127.8, 127.6, 124.2, 120.7, 118.3, 111.3, 109.5, 69.6, 62.2, 51.7, 50.8, 48.5, 36.1, 34.4; MS (ESI) *m/z*: 427 ($M+H^+$, 100); HRMS (ESI): calculated for $C_{23}H_{23}ClN_2O_4$: 426.1346, found 426.1343.

4.2.3. General procedure for the synthesis of aminocarbothiol- pyrrolidines ***(7j-o)****.*

A solution of benzoyl isothiocyanate (0.213 mL, 1.3 mmol) in dry acetonitrile (15 mL) was added dropwise to a solution of the corresponding pyrrolidine (1.2 mmol) in dry acetonitrile (25 mL). The resulting solution was stirred at room temperature for 8-24 h. After completion of the reaction by monitoring TLC, the solvent removed and purified by flash chromatography.

4.2.3.1. Methyl (1R,3S*,3aR*,6aS*)-1-[(1H-indol-3-yl)methyl]-2-(benzoylcarbamothioyl)-4,6-dioxo-3,5-diphenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate* ***(7j)****:* Pale yellow solid (552 mg, 86%); mp: 164-166 ºC (diethyl ether); IR ν_{max}: 3344, 3251, 3063, 2952, 2848, 1787, 1720, 1596 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 11.32 (s, 1H, NH), 10.54 (s, 1H, NH), 8.02 (s, 1H, Ar*H*), 7.70 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.50-7.05 (m, 16H, Ar*H*), 6.67-6.65 (m, 2H, Ar*H*), 5.72 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 15.3 Hz, 1H), 3.91 (d, *J* = 9.4 Hz, 1H), 3.81-3.75 (m, 4H), 2.91 (dd, *J* = 11.1 Hz, 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 180.6 (CS), 173.4 (CO), 172.0 (CO), 168.0 (CO), 164.8 (CO), 137.0, 136.8, 132.8, 132.1, 131.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.8, 126.4, 125.8, 121.1, 119.1, 117.9, 111.5, 106.8, 78.3, 68.7, 52.5, 52.1, 49.6, 27.1; MS (ESI) *m/z*: 643.2 (M^+ + 1, 100); HRMS (ESI-TOF-MS) calculated for $C_{37}H_{30}N_4O_5S$): 642.1937, found 642.1930.

4.2.3.2. Methyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-2-(benzoylcarbamothioyl)-3-(2,4-dichlorophenyl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate* ***(7k)****:* Pale yellow prisms (605 mg, 85 %); mp 154-156 ºC (from EtOAc:hexane); IR (ν_{max}): 3387, 2951, 2920, 2851, 1783, 1716, 1593, 1559 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.48 (br. s, 1H, NH), 8.18 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.92 (d, *J* = 8.2 Hz, 1H Ar*H*), 7.72 (d, *J* = 7.7 Hz, 1H), 7.62-7.06 (m, 12H, Ar*H*), 6.57 (d, *J* = 7.3 Hz, 2H, Ar*H*), 5.94 (d, *J* = 15.2 Hz, 1H), 4.45 (d, *J* = 15.0 Hz, 1H), 4.01 (d, *J* = 15.2 Hz, 1H), 3.94-3.89 (m, 3H,), 3.87 (s, 3H, OCH_3), 2.63 (dd, *J* = 10.4 Hz, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 181.4 (CS), 173.5, 171.8, 168.1, 164.1 (CO), 138.8, 134.5, 133.8, 133.0, 132.5, 132.2, 131.7, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 126.4, 125.9, 121.2, 119.2, 117.7, 111.6, 106.7, 78.9, 66.0, 52.4, 48.5, 26.8, 15.1. MS (ESI) *m/z*: 710.8 (M^+-1, 100), 711.8 (40); HRMS (ESI): calculated for $C_{37}H_{28}Cl_2N_4O_5S$: 711.1157, found 711.1167.

4.2.3.3. Ethyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-2-(benzoylcarbamothioyl)-3-(4-chlorophenyl)-5-cyclohexyl-4,6-dioxo-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate* ***(7l)***: Pale yellow prisms (558 mg, 80%); mp 148-150 ºC (from EtOAc:hexane); IR ν_{max}: 3385, 2931, 1739, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.44 (br. s, 1H, NH, minor rotamer), 8.34 (br. s, 1H, NH major rotamer), 8.10-7.03 (m, 30H, Ar*H*, NH major and minor rotamer), 5.65 (d, *J* = 11.6 Hz, 1H, minor rotamer), 5.44 (d, *J* = 11.2 Hz, 1H, major rotamer), 4.79 (d, *J* = 15.5, 1H, minor rotamer), 4.43-4.21 (m, 4H, major and minor rotamer), 4.40 (d, *J* = 14.5, 1H, major rotamer), 3.92 (d, *J* = 15.0 Hz, 1H, major rotamer), 3.87 (d, *J* = 15.5, 1H, minor rotamer), 3.50-3.45 (m, 2H, major and minor rotamer), 2.74 (dd, *J* = 11.2, 10.1 Hz, 1H, minor rotamer), 2.41 (dd, *J* = 11.2 Hz, 9.1 Hz, 1H, major rotamer), 1.86-0.81 (m, 22H, major and minor rotamer), 1.47 (t, *J* = 7.08 Hz, 3H, major rotamer), 1.33 (t, *J* = 7.0 Hz, 3H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 187.2 (CS major rotamer), 178.6 (CS minor rotamer), 174.1 (CO minor rotamer), 173.7 (CO major rotamer), 173.2 (CO major rotamer), 173.0 (CO minor rotamer), 172.1 (CO major rotamer), 169.6 (CO major rotamer), 167.9 (CO minor rotamer), 163.8 (CO minor rotamer), 135.9 (major rotamer), 135.8 (minor rotamer), 135.0 (major rotamer), 134.7 (minor rotamer), 134.4 (minor rotamer), 133.8 (major rotamer), 133.5 (major rotamer), 133.1 (major rotamer), 133.0 (major rotamer), 132.3 (minor rotamer), 131.7 (minor rotamer), 131.7 (minor rotamer), 129.2 (minor rotamer), 128.7 (minor rotamer), 128.6 (major rotamer), 128.6 (minor rotamer), 128.2 (major rotamer), 127.8 (major rotamer), 127.6 (major rotamer), 127.0 (minor rotamer), 125.8 (minor rotamer), 124.3 (major rotamer), 122.7 (major rotamer), 122.3 (minor rotamer), 120.5 (major rotamer), 120.2 (minor rotamer), 118.0 (minor rotamer), 117.9 (major rotamer), 111.8 (major rotamer), 111.7 (minor rotamer), 108.7 (major rotamer), 108.2 (minor rotamer), 77.2 (minor rotamer), 76.0 (major rotamer), 68.9 (minor rotamer), 68.2 (major rotamer), 66.9 (minor rotamer), 62.4 (major rotamer), 53.9 (minor rotamer), 52.0 (major rotamer), 51.9 (major rotamer) 49.0 (minor rotamer), 47.4 (major rotamer), 32.9 (minor rotamer), 28.3 (major rotamer), 28.3 (minor rotamer), 27.9 (minor rotamer), 27.7 (minor rotamer), 27.5 (minor rotamer), 25.6 (minor rotamer), 25.5 (major rotamer), 24.7 (major rotamer), 14.0 (major rotamer); MS (ESI) *m/z*: 696 (M^+ - 1, 100), 694 (35); HRMS (ESI-TOF-MS) calculated for $C_{38}H_{38}ClN_4O_5S$: $[MH]^+$ 697.2251 (Cl:35), found 697.2253 (Cl:35), 699.2269 (Cl:37).

4.2.3.4. Dimethyl (2R,4S*,5R*)-1-(benzoylcarbamothioyl)-2-benzyl-5-(2,4-dichlorophenyl)pyrrolidine-2,4-dicarboxylate (**7m**)*:[35]

4.2.3.5. Dimethyl (2R,4S*,5R*)-1-(benzoylcarbamothioyl)-5-(4-chlorophenyl)-2-phenylpyrrolidine-2,4-dicarboxylate (**7n**)*: Pale yellow prisms, (495 mg, 92%); m.p.: 162-165 ºC (from diethyl ether), 2:1 rotamer mixture; IR υ_{max}: 3278, 3072, 2981, 1953, 1743, 1675, 1596 cm^{-1}; ; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.91-7.23(m, 30H, NH, Ar*H* major and minor rotamers), 5.92 (d, *J* = 8.4 Hz, 1H, major rotamer), 5.89 (d, *J* = 8.4 Hz, 1H, minor rotamer), 3.92 (s, 3H, OCH_3, major rotamer), 3.71 (s, 3H, OCH_3, minor rotamer), 3.46-3.14 (m, 4H, major and minor rotamers), 3.39 (s, 3H, OCH_3, minor rotamer), 3.29 (s, 3H, OCH_3, major rotamer), 2.72-2.54 (m, 2H, major and minor rotamers); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 187.5 (CS, minor rotamer), 180.2 (CS, major rotamer), 172.2 (CO, minor rotamer), 171.4 (CO, minor rotamer), 170.2 (CO, major rotamer), 169.0 (CO, minor rotamer), 168.7 (CO, major rotamer), 164.7 (CO, major rotamer), 138.0, 135.6, 134.5, 134.4, 133.6, 133.3, 133,1, 132.8, 132.3, 132.1, 129.3, 129.1, 129.1, 129.0, 128.8, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.5, 127.3, 126.2, 125.4, 78.6, 75.5, 67.0, 66.3, 53.4, 53.1, 51.8, 51.7, 57.1, 46.3, 41.2, 41.0. MS (ESI) *m/z*: 535.1 (M^+-1, 100), 537.1 (35). Anal. Calc. for $C_{28}H_{25}ClN_2O_5S$: C, 62.62; H, 4.69; N, 5.22; S, 5.97. Found: C, 62.89; H, 5.02; N, 5.00; S, 5.74.

4.2.3.6. Dimethyl (2R,4S*,5R*)-2-[(1H-indol-3-yl)methyl]-1-(benzoylcarbamothioyl)-5-(4-chlorophenyl)pyrrolidine-2,4-dicarboxylate (**7o**)*: Pale yellow prisms (472 mg, 80 %); mp 129-131 ºC (from diethyl ether, decomp.); IR ν_{max}: 3357, 2948, 2922, 2850, 1731, 1559 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.38 (s, 1H, NH major rotamer), 8.28 (s, 1H, NH minor rotamer), 8.17-7.01 (m, 28H, Ar*H* major and minor rotamer), 5.39 (d, *J* = 10.2 Hz, 1H, major rotamer), 5.30 (d, *J* = 9.7 Hz, 1H minor rotamer), 4.55 (d, *J* = 15.4 Hz, 1H major rotamer), 4.22 (d, *J* = 15.8 Hz, 1H, minor rotamer), 3.94 (s, 3H, OCH_3 major rotamer), 3.81 (s, 3H, OCH_3 minor rotamer), 3.77-3.68 (m, 2H, major and minor rotamer), 3.08 (s, 3H, OCH_3 minor rotamer), 3.00 (s, 3H, OCH_3 major rotamer), 2.98-2.93 (m, 2H, major and minor rotamer), 2.64-2.47 (m, 2H, major and minor rotamer); 2.45-2.40 (m, 2H, major and minor rotamer); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 185.5 (CS, minor rotamer), 178.4 (CS, major rotamer), 173.5 (CO, minor rotamer), 172.0 (CO, major rotamer), 169.6 (CO, minor rotamer), 169.3 (CO, major rotamer), 164.1 (CO, minor rotamer), 164.1 (CO, major rotamer), 136.0 (minor rotamer), 135.8 (minor rotamer), 134.4 (minor rotamer), 133.5 (minor rotamer), 133.3 (minor rotamer), 133.0 (minor rotamer), 132.6 (minor rotamer), 129.7 (minor rotamer), 129.1 (major rotamer), 128.7 (major rotamer), 128.5 (minor rotamer), 128.0 (major rotamer), 127.6 (major rotamer), 125.4 (minor rotamer), 123.6 (minor rotamer), 122.5 (minor rotamer), 122.1 (minor rotamer), 120.3 (minor rotamer), 120.0 (minor rotamer), 118.3 (minor rotamer), 111.4 (major rotamer), 110.3 (minor rotamer), 109.5 (minor rotamer), 73.7 (major rotamer), 71.2 (minor rotamer), 68.0 (major rotamer), 67.5 (minor rotamer), 52.9 (minor rotamer), 51.4 (major rotamer), 47.2 (major rotamer), 45.7 (minor rotamer), 37.2 (major rotamer), 36.4 (minor rotamer), 31.2 (major rotamer), 26.4 (minor rotamer), 25.3 (minor rotamer), 22.6 (major rotamer); MS (ESI) *m/z*: 590 (M, 100), 591 (39); HRMS (ESI): calculated for $C_{31}H_{28}ClN_3O_5S$: 589.1438, found 589.1437.

*4.2.4. General procedure for the synthesis of pyrrolidine-thiazoles (**5j-o**).*

2-Bromo-4'-methoxyacetophenone (320 mg, 1.4 mmol), dissolved in dry acetone (10 mL), was added dropwise to a solution of aminocarbothiolpyrrolidine (1 mmol) in dry acetone (10 mL), the resulting mixture was refluxed for 24–48 h (monitoring by TLC). The reaction was cooled down, the solvent evaporated, ethyl acetate was added (15 mL) and the resulting organic phase washed with bine, dried and evaporated. The crude product was purified by flash chromatography**.**

4.2.4.1. Methyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl)]-2-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-4,6-dioxo-3,5-diphenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5j**)*: Yellow prisms (502 mg, 65 %); mp 148-150 ºC (diethyl ether, decomp.); IR ν_{max}: 3439, 3057, 2954, 1785, 1734, 1712, 1593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.36 (s, 1H, NH), 7.85 (s,1H, Ar*H*), 7.53-7.06 (m, 18H, Ar*H*), 6.79 (s, 1H, Ar*H*), 6.60-6.55 (m, 4H, Ar*H*), 4.72 (d, *J* = 10.9 Hz, 1H), 4.66 (d, *J* = 15.1 Hz, 1H), 3.97 (s, 3H, OCH_3), 3.94 (d, *J* = 8.9 Hz, 1H), 3.77 (d, *J* = 15.2 Hz, 1H), 3.71 (s, 3H, OCH_3), 2.82 (t, *J* = 9.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 187.8 (CO), 173.2 (CO), 172.3 (CO), 170.2, 165.2, 162.7, 155.9, 136.0, 134.8, 134.5, 131.9, 130.9, 130.2, 130.1, 129.1, 128.9, 128.6, 127.7, 127.7, 125.8, 124.6, 123.8, 122.8, 120.6, 117.9, 113.0, 111.9, 109.4, 69.2, 55.3,54.5, 53.1, 49.8, 29.5; MS (ESI) *m/z*: 773 (M^+ + 1, 100); HRMS (ESI): calculated for $C_{46}H_{36}N_4O_6S$: 772.2356, found 772.2367.

4.2.4.2. Methyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-3-(2,4-dichlorophenyl)-2-(5-(4-methoxybenzoyl)-4-phenyl-4,5-dihydrothiazol-2-yl)-4,6-dioxo-5-phenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5k**)*: Pale yellow prisms, (690 mg, 82 %); mp 166-168 ºC (diethyl ether, decomp.). IR ν_{max}: 2951, 2922, 2851, 1788, 17.19, 1596, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.39 (s, 1H, NH), 7.92 (d, *J* = 8.4 Hz, 1H, Ar*H*), 7.58 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.51 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.43 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.37-7.08 (m, 12H, Ar*H*), 6.78 (s, 1H, Ar*H*), 6.71 (d, *J* = 7.3 Hz, 2H, Ar*H*), 6.59 (d, *J* = 8.4 Hz, 2H, Ar*H*), 5.23 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 15.2 Hz, 1H), 3.97 (m, 4H, OCH_3), 3.78 (d, *J* = 15,2 Hz, 1H), 3.72 (s, 3H, OCH_3), 2.89 (t, *J*= 10.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 187.6 (CO), 173.1 (CO), 171.6 (CO), 170.2 (CO), 164.6, 162.9, 155.8, 136.0, 135.8, 135.6, 134.4, 132.0, 131.5, 130.0, 129.1, 129.0, 128.7, 128.6, 127.9, 127.9, 127.7, 125.9, 125.4, 123.8, 122.9, 120.7, 117.8, 113.1, 111.92, 109.8, 64.9, 55.3, 54.3, 53.2, 48.7, 29.3; MS (ESI) *m/z*: 843 (M + 2, 100). HRMS (ESI): calculated for $C_{46}H_{34}Cl_2N_4O_6S$): 841.7600, found 841.7610.

4.2.4.3. Ethyl (1S,3R*,3aS*,6aR*)-1-[(1H-indol-3-yl)methyl]-3-(4-chlorophenyl)-5-cyclohexyl-2-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-4,6-dioxo-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (**5l**):*): Pale yellow prisms (639 mg, 76 %); mp 161-163 ºC (from diethyl ether); IR ν_{max}: 3367, 2933, 2857, 1781, 17.42, 1705, 1597, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H: 8.46 (s, 1H, NH), 7.71 (d, *J*= 6.4 Hz, 1H, Ar*H*), 7.49-7.04 (m, 14H, Ar*H*), 6.74 (s, 1H, ArH), 6.58 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.57 (d, *J* = 15.1 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.44-4.38 (m, 2H), 3.71 (m, 5H), 2.82 (t, *J* = 10.1 Hz, 1H), 1.84-0.86 (m, 11H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 187.8 (CO), 174.3 (CO), 173.3 (CO), 169.9 (CO), 165.0, 162.8, 156.0, 136.1, 134.9, 134.4, 133.5, 132.0, 130.2, 130.1, 128.7, 127.7, 124.5, 123.9, 122.6, 120.4, 118.0, 113.1, 111.8, 109.2, 76.1, 68.2, 62.3, 55.4, 54.0, 52.1, 49.4, 29.5, 28.4, 27.9, 25.6, 24.8, 14.2; MS (ESI) *m/z*: 827 (M, 100), 828 (55); HRMS (ESI): calculated for: $C_{47}H_{43}ClN_4O_6S$: 827.3930, found 827.3937.

4.2.4.4. Dimethyl (2R,4S*,5R*)-2-benzyl-5-(2,4-dichlorophenyl)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)pyrrolidine-2,4-dicarboxylate (**5m**):* Pale yellow prisms (594

mg, 83 %); as: mp 115-117 ºC (from EtOAc:hexane, decomp.); IR ν_{max}: 2951, 2920, 2839, 1739, 1595, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.04 (d, *J* = 9.0 Hz, 1H, Ar*H*), 7.47-7.04 (m, 14H, Ar*H*), 6.56 (d, *J* = 7.9 Hz, 2H, Ar*H*), 5.11 (d, *J* = 9.7 Hz, 1H), 4.27 (d, *J* = 14.2 Hz, 1H), 3.88 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.56 (d, *J* = 14.3 Hz, 1H), 3.18 (s, 3H, OCH_3), 3.01 (t, *J* = 11.8 Hz, 1H), 2.40-2.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 190.0 (CO), 187.7 (CO), 173.6 (CO), 169.8, 164.7, 164.2, 162.7, 156.6, 136.7, 131.9, 131.4, 130.6, 130.2, 130.1, 129.9, 129.1, 128.5, 128.0, 127.8, 127.6, 114.1, 113.0, 73.0, 63.1, 53.1, 51.7, 46.8, 38.0, 37.2, 30.8; MS (ESI) *m/z*: 715 (M, 100), 716 (42); HRMS (ESI): calculated for $C_{38}H_{32}Cl_2N_2O_6S$: 715.6420, found 715.6427.

4.2.4.5. Dimethyl (2R,4S*,5R*)-5-(4-chlorophenyl)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)-2-phenylpyrrolidine-2,4-dicarboxylate (**5n**):* Pale yellow prisms (467 mg, 70 %); mp 122-124 ºC (diethyl ether); IR ν_{max}: 2952, 2922, 2852, 1735, 1595, 1572, 1509 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.67 (d, *J*= 8.0 Hz, 2H, Ar*H*), 7.43 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.38-7.27 (m, 9H, Ar*H*), 7.12-6.96 (m, 5H, Ar*H*), 6.55 (d, *J* = 12.0 Hz, 2H, Ar*H*), 5.21 (d, *J* = 8.0 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.39 (d, *J* = 4.0 Hz, 2H), 3.33 (s, 3H, OCH_3), 2.59-2.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C : 187.5 (CO), 171.6 (CO), 169.1 (CO), 165.2, 162.6, 156.3, 137.6, 134.8, 134.5, 134.3, 131.8, 130. 3, 129.9, 129.8, 128.9, 128.3, 128.0, 127.7, 127.5, 127.4, 124.4, 113.0, 75.0, 66.1, 55.3, 53.1, 51.7, 47.7, 41.7; MS (ESI) *m/z*: 667 (M, 100), 668 (37). HRMS (ESI-TOF-MS): calcd. for $C_{37}H_{32}ClN_2O_6S$ $[MH]^+$ 667.1670; found 667.1688.

4.2.4.6. Dimethyl (2R,4S*,5R*)-2-((1H-indol-3-yl)methyl)-5-(4-chlorophenyl)-1-(5-(4-methoxybenzoyl)-4-phenylthiazol-2-yl)pyrrolidine-2,4-dicarboxylate (**5o**)*: Pale yellow prisms (540 mg, 75 %); mp 145-147 ºC (diethyl ether); IR ν_{max}: 2952, 2921, 2852, 1737, 1595, 1511 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.32 (s, 1H, NH), 7.50-7.07 (m, 15H, Ar*H*), 6.81 (d, *J* = 2.2 Hz, 1H, Ar*H*), 6.59-6.57 (m, 2H, Ar*H*), 4.50 (d, *J* = 9.9 Hz, 1H), 4.35 (d, *J* = 15.9 Hz, 1H), 3.92 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.56 (d, *J* = 15.9 Hz, 1H), 3.08 (s, 3H, OCH_3), 3.02 (t, *J* = 12.0 Hz, 1H), 2.68-2.60 (m, 1H), 2.46 (dd, *J* = 12.9, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 187.7 (CO), 173.8 (CO), 169.6 (CO), 165.2, 162.6, 156.5, 136.0, 134.8, 134.7, 134.4, 131.8, 130.5, 130.0, 130.0, 128.5, 128.4, 128.0, 127.6, 123.9, 123.3, 122.4, 120.1, 118.2, 113.0, 111.5, 100.7, 73.3, 67.8, 55.3, 52.9, 51.5, 47.6, 37.4, 28.0; MS (ESI) *m/z*: 720 (M, 100); HRMS (ESI): calculated for $C_{40}H_{34}ClN_3O_6S$: 720.2371, found 720.2367.

*4.2.5. General procedure for the synthesis of pyrrolidine-thiazole (**9n-o**).*

2-Bromo-4′-methoxyacetophenone (320 mg, 1.4 mmol), dissolved in dry methanol (10 mL), was added dropwise to a solution of aminocarbothiolpyrrolidine (1 mmol) in dry methanol (10 mL), the resulting mixture was refluxed for 24–48 h (monitoring by TLC). The reaction was cooled down, the solvent evaporated, ethyl acetate was added (15 mL) and the resulting organic phase washed with bine, dried and evaporated. The crude product was purified by flash chromatography

4.2.5.1. (2R,4S*,5R*)-dimethyl 5-(4-chlorophenyl)-1-[4-(4-methoxyphenyl)thiazol-2-yl]-2-phenylpyrrolidine-2,4-dicarboxylate (**9n**):* White solid (405 mg, 72 %); mp: 197-199 ºC (diethyl ether); IR ν_{max}: IR ν_{max}: 2952, 2920, 2855, 1737, 1591, 1570, 1507 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 7.65 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.53 (d, *J* = 4.0 Hz, 2H, Ar*H*), 7.50-6.76 (m,7H, Ar*H*), 6.76 (d, *J* = 4.0 Hz, 2H, Ar*H*), 6.52 (s, 1H), 5.18 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.36 (d, *J* = 4.0 Hz, 2H), 3.32 (s, 3H, OCH_3), 2.55-2.47 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 172.2 (CO), 169.5 (CO), 163.3, 159.1, 151.1, 138.1, 135.5, 134.4, 129.7, 128.6, 127.8, 127.7, 127.7, 127.2, 113.7, 100.4, 74.6, 65.6, 55.2, 53.0, 51.7, 47.8, 41.4; MS (ESI) *m/z*: 563 (M, 100), 564 (33); HRMS (ESI-TOF-MS): calcd. for $C_{30}H_{28}ClN_2O_5S$ $[MH]^+$ 563.1407; found 563.1422.

4.2.5.1. Dimethyl (2R,4S*,5R*)-2-[(1H-indol-3-yl)methyl]-5-(4-chlorophenyl)-1-(4-(4-methoxyphenyl)thiazol-2-yl)pyrrolidine-2,4-dicarboxylate (**9o**)*): White prisms (499 mg, 82%); mp 247-249 ºC (EtOAc:hexane, decomp.); IR ν_{max}: 3371, 2950, 2924, 2841, 1735, 1521 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 8.10 (s, 1H, NH), 7.76 (m, 2H, Ar*H*), 7.48-6.89 (m, 10H, Ar*H*), 6.77 (m, 1H, Ar*H*), 6.58 (s, 1H), 4.46 (d, *J*= 9.9 Hz, 1H), 4.41 (d, *J*= 15.0 Hz, 1H), 3.91 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.56 (d, *J*= 15.0 Hz, 1H), 3.08 (s, 3H, OCH_3), 3.00 (t, *J* = 12.7 Hz, 1H), 2.64 (dd, *J* = 19.7, 8.5 Hz, 1H), 2.42 (dd, *J* = 12.8 Hz, 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 174.5 (CO), 169.9 (CO), 163.3 (CO), 159.2, 151.2, 136.1, 135.9, 134.0, 129.9, 128.5, 128.2, 128.1, 127.9, 127.2, 123.3, 122.2, 120.0, 118.6, 113.9, 111.2, 100.1, 72.9, 67.1, 55.3, 52.7, 51.4, 47.7, 37.1, 27.4; MS (ESI) *m/z*: 616 (M^+, 100), 617 (37). HRMS (ESI): calculated for $C_{33}H_{30}ClN_3O_5S$: 616.1290, found 616.1280.

Acknowledgements

This work is a part of Samet Belveren's ongoing PhD thesis granted by Mersin University (Project no. BAP-SBE TEB(SB) 2017-2-TP3-2564). The authors thank Mersin University (Turkey) and the University of Alicante for support. We also thank the Scientific and Technological Research Council of Turkey (TÜBİTAK), the Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI) and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P, and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEOII/2014/017), (Consolider Ingenio 2010, CSD2007-00006) for research financing.

Table 3. The MIC values (μg/mL) of the targed compounds against the bacteria and *M. tuberculosis* H37Rv strain.

Compound	*Staphylococcus Aureus* (ATCC 25925)	*Escherichia coli* (ATCC 25923)	*Acinetobacter baumannii* (ATCC 02026)	*Bacillus subtilis* (ATCC 6633)	*Aeromonas Hydrophila* (ATCC 95080)	*M. tuberculosis* H37RV
6m	500 µg/ml	250 µg/ml	125 µg/ml	250 µg/ml	500 µg/ml	62.5 µg/ml
7m	250 µg/ml	250 µg/ml	125 µg/ml	125 µg/ml	125µg/ml	7.81 µg/ml

7n	250 µg/ml	250 µg/ml	125 µg/ml	62,5 µg/ml	125 µg/ml	31.25 µg/ml
6j	250 µg/ml	125 µg/ml	62,5 µg/ml	125 µg/ml	125 µg/ml	20 µg/ml
6l	250 µg/ml	250 µg/ml	125 µg/ml	250 µg/ml	500 µg/ml	3.25 µg/ml
6o	250 µg/ml	250 µg/ml	125 µg/ml	250 µg/ml	250 µg/ml	**1.95 µg/ml**
7k	250 µg/ml	500 µg/ml	125 µg/ml	125 µg/ml	250µg/ml	7.81 µg/ml
7l	250 µg/ml	250 µg/ml	125 µg/ml	125 µg/ml	250 µg/ml	3.90 µg/ml
7o	250 µg/ml	250 µg/ml	125 µg/ml	125 µg/ml	125 µg/ml	**0.24 µg/ml**
5m	500 µg/ml	500 µg/ml	125 µg/ml	250 µg/ml	500 µg/ml	62.5 µg/ml
9o	500 µg/ml	125 µg/ml	125 µg/ml	250 µg/ml	250 µg/ml	**0.48 µg/ml**
5l	250 µg/ml	250 µg/ml	125 µg/ml	250 µg/ml	250 µg/ml	62.5 µg/ml
Ampicillin	31.25	15.62	125	0.9	31.25	
Isoniazid						0.2 and 1 µg/ml
Ethambutol						5 and 10 µg/ml

MIC: Minimum Inhibitory Concentrations

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